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BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Application Number: 10/663,533
Filing Date: September 16, 2003
Appellant(s): GILBERT ET AL.

Wendy Choi

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on April 11, 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 26, 33-52 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Wijngaarden et al. Recl. Trav. Chim. Pays-Bas, 1993, Vol. 112, pages 126-130.

Barnes et al. Neuropharmacology, 1999, Vol. 38, pages 1083-1092.

Fletcher et al. Psychopharmacology, 1990, Vol. 100, No. 2, pages 188-94, abstract.

Matuszewich et al. Brain Research, 1999, Vol. 820, No. 1-2, pages 55-62, abstract.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 26, 33-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

a. ***Nature of the invention.***

The instant invention is drawn to the method of using a benzo[1,4]dioxin-azabicyclo[3.2.1]octane compound in the treatment of Alzheimer's disease, appetite control, disorders of thermoregulation, and sleep dysfunction.

b. ***State of the prior art and the level of the skill in the art.***

5-HT receptors are known to have subclasses differing in their structures, regional distribution, pharmacology, modes of actions, and functions (Wijngaarden et al. Recl. Trav. Chim. Pays-Bas, 1993, 112:126-130; Barnes et al. Neuropharmacology, 1999, 38: 1083-1092, pages 1085-6). While $5HT_{1A}$ receptor has been implicated in many physiological responses, and $5HT_{1A}$ receptor agonist has been shown to have anxiological and antidepressant activity, the nexus between Alzheimer's disease, appetite control, disorders of thermoregulation, sleep dysfunction, and $5HT_{1A}$ receptor antagonism has not been predictably established. For example, while $5HT_{1A}$ receptor agonist evokes hypothermia, inhibition of 5HT synthesis and 5-HT lesions do not prevent hypothermia when the agonists are injected in rats (Barnes, page 1092). Some of the responses elicited by a $5HT_{1A}$ receptor agonist, 8-OH-PAT, such as hyperphagia (Fletcher et al. Psychopharmacology, 1990, 100(2): 188-94, abstract), altered sexual behavior (Matuszewich et al. Brain Research 1999, 820(1-2): 55-62, abstract), are not reversed by a $5HT_{1A}$ receptor antagonist, thereby suggesting that these effects are not mediated by the $5HT_{1A}$ receptor, and that agonism/antagonism is not straight-forward and predictable.

At the time of the invention, there is no umbrella drug known to be effective in treating all the diseases/conditions as recited.

The level of the skill in the 5-HT_{1A} receptor antagonist art is high.

c. ***Predictability/unpredictability of the art.***

The high degree of unpredictability is well recognized in the 5-HT receptor ligand art. A slight change in the structure of the compound would drastically alter its affinity and selectivity (Wijngaarden, Recl. Trav. Chim. Pays-Bas, 1993, 112:126-130, pages 129-130, Fig. 6, Fig. 7, Fig. 8). The in vitro binding data do not necessarily reflect the in vivo activity under the much more complex physiological conditions.

d. ***Amount of guidance/working examples.***

Preparation of example compounds has been described.

The procedures for the 5-HT transporter binding assays, 5-HT_{1A} receptor binding assays, and the assay for the assessment of the antagonist activity, are found on pages 9-10 of the specification. Results are shown for Examples 1-11 on page 11 of the specification.

No in vivo procedures are described. The specific conditions wherein the inventive compound may be used for seemingly opposite conditions within the general appetite control, disorders of thermoregulation, and sleep dysfunction is not described in the specification.

e. ***The breadth of the claims.***

Applicant's assertion that all the inventive compounds would be effective in treating Alzheimer's disease, appetite control (including the conflicting hyperphagia and hypophagia), any disorder of thermoregulation (including the opposing hypothermia and hyperthermia), any sleep dysfunction (including the conflicting insomnia and narcolepsy) is not commensurate with the scope of the objective enablement, especially in view of the

high degree of unpredictability in the art, the limited working examples and the non-establishment of the nexus between the antagonism of $5HT_{1A}$ receptor and the recited disorders (paragraphs b, c, d above).

f. ***Quantitation of undue experimentation.***

Since the instant 'appetite control', 'disorders of thermoregulation', 'sleep dysfunction', etc. are general classes of disorders embracing opposing and conflicting conditions arising from diverse origins under different conditions, one of ordinary skill in the art would not predictably be able to use a single $5HT_{1A}$ receptor antagonist compound of the instant to treat all these diverse and contradictory disorders in the absence of any description or guidance on the specific conditions of operation for these conflicting conditions. Furthermore, in view of the high degree of unpredictability in the art, the limited working examples and the fact that the breadth of the claims is not commensurate with that of the objective enablement, the disclosure as presented would not allow one of ordinary skill in the art to use the invention as claimed without undue experimentation, especially when the nexus between the antagonism of $5HT_{1A}$ receptor and the recited disorders has not been fully established at the time of the invention (paragraphs b-e above).

(11) Response to Argument

a. ***Nexus between 5-HT1A Receptor antagonists and Treatment of Alzeheimer's disease, appetite control, disorders of thermoregulation and sleep dysfunction.***

In view of the findings of Barnes, Fletcher and Matuszewich, the examiner has raised the issue that at the time of the invention, the nexus between the treatment of the recited diseases and the antagonism of $5HT_{1A}$ receptor has not been predictably established. More specifically, while $5HT_{1A}$ receptor agonist evokes hypothermia, inhibition of 5HT synthesis and 5-HT lesions do not prevent hypothermia when the agonists are injected in rats (Barnes, page 1092). Some of the responses elicited by a $5HT_{1A}$ receptor agonist, 8-OH-PAT, such as hyperphagia (Fletcher et al. Psychopharmacology, 1990, 100(2): 188-94, abstract), altered sexual behavior (Matuszewich et al. Brain Research 1999, 820(1-2): 55-62, abstract), are not reversed by a $5HT_{1A}$ receptor antagonist, thereby suggesting that these effects are not mediated by the $5HT_{1A}$ receptor and simple agonism/antagonism at the $5HT_{1A}$ receptor is not predictive of disease outcome in vivo.

Appellants have not addressed the above references but just cited the following references: Lanfumey et al. and Kwon et al. (published in 2004, which is after the instant effective filing date) for Alzheimer's disease, Moreau et al. for appetite control, Ootsuka et al. for disorders of thermoregulation and Sorensen et al. for sleep dysfunction. While these references may suggest the involvement of $5\text{-}HT_{1A}$ receptor in these diseases, they do not negate the findings of Barnes and Fletcher. They do not teach what the receptor involvement is and they do not teach that antagonism of $5HT_{1A}$ would have a predictable, therapeutic outcome on the scope of diseases and symptoms encompassed by the

instantly broadly claimed methods. The nexus between treatment of Alzheimer's disease, appetite control, disorders of thermoregulation, sleep dysfunction and the antagonism of $5HT_{1A}$ receptor therefore is not predictably established in view of the controversial evidence of Barnes and Fletcher.

In response to the submission of the above references, it is the examiner's position that even if the $5HT_{1A}$ receptor antagonist may abolish the body temperature decrease upon 5 HT_{1A} activation (Ootsuka et al), may induce a decrease in REM sleep (Sorensen et al), or may decrease palatable food consumption in rats (Moreau et al), there is little support for the use of $5HT_{1A}$ antagonist for treating all types of 'appetite control' (which encompass the opposing hyperphagia and hypophagia), any 'disorders of thermoregulation' (which includes the opposing hypothermia and hyperthermia), all forms of 'sleep dysfunction' (which covers both insomnia and narcolepsy) as encompassed and recited in the instant claims. Since these are general classes of disorders embracing opposing and conflicting conditions arising from diverse origins, one of ordinary skill in the art would not reasonably expect to use a single $5HT_{1A}$ receptor antagonist compound of the instant to treat all these contradictory disorders.

Moreover, in the instant $5HT_{1A}$ antagonist art, a high degree of unpredictability exists in that slight change in the structure of the compound would drastically alter its affinity and selectivity (Wijngaarden, Recl. Trav. Chim. Pays-Bas, 1993, 112:126-130, pages 129-130, Fig. 6, Fig. 7, Fig. 8). The in vitro binding data do not necessarily reflect the in vivo activity. In the highly unpredictable pharmaceutical art, the required disclosure will be greater than for the disclosure of an invention involving a predictable

factor such as a mechanical or electrical element. In re Vaeck, 20 USPQ 2d 1438. Since the above studies (and the studies described in Lanfumey et al. and Kwon et al) are based on $5HT_{1A}$ antagonists structurally removed from the instant compound, one of ordinary skill in the art has little basis to extend the data in these references to the instant.

With the filing of this Brief, Appellants have submitted ***7 new references***. If these references were to provide prima facie support for the claims, they should have been submitted in the earlier stages of the prosecution. In reality, these references fail to provide the required support for the following reasons.

Alzheimer's disease.

The Schechter reference was published *after* the effective filing date of the instant application and is therefore not reflective of the state of the art. Further, Schechter only describes the ***potential*** utility of 5-HT_{1A} receptor antagonists in the treatment of a single symptom, i.e. the cognitive dysfunction, that is associated with Alzeheimer's disease. Schechter does not support the predictable use these claimed compounds to effectively treat Alzeheimer's disease in general nor to treat the breadth of disorders and symptoms encompassed by the instant claims.

Appetite control

Ebenezer et al. teaches that the 5-HT_{1A} agonist, 8-OH-DPAT, has complex effects on feeding behavior in pigs in that it elicits hyperphagic and hypophagic effects in

satiated and fasted pigs respectively, which effects are abolished by the $5HT_{1A}$ antagonist, WAY 100635. However, WAY 100635 by itself, however, has no significant effects on feeding, which is different from the findings of Moreau et al. , who show that the 5-HT_{1A} antagonist, (S)-UH-301, decreases palatable food consumption in rats by itself. These references highlight the unpredictability of the art, and caution the extrapolation of results from one antagonist to another antagonist compound. Furthermore, neither Ebenezer nor Moreau suggests the use of $5HT_{1A}$ antagonist for appetite control (both hyperphagia and hypophagia arising from any conditions) in a human as recited in the instant.

Disorders of thermoregulation

Brubacher et al. state that hyperthermia is part of the syndrome of serotonin excess in response to excessive stimulation of $5HT_{1A}$ receptor. However, whether the antagonist of $5HT_{1A}$ would abolish the effect has not been shown. Brubacher's description is therefore at variance with the findings of Oerther et al. that hypothermia is caused by the 5-HT_{1A} agonist, 8-OH-DPAT. Contrary to Appellants' contention that these references lend support to the use of a 5HT1A receptor antagonist for treatment of any disorders of thermoregulation (including hypothermia and hyperthermia), they only demonstrate the controversial role of 5-HT1A receptor in thermoregulation.

Sleep dysfunction

While Bjorvatn et al. demonstrates that systemic administration of $5HT_{1A}$ agonist increases wakefulness and reduces slow wave sleep and REM sleep, and Gillin shows that a relatively selective $5HT_{1A}$ agonist, ipsapiraone, inhibits REM sleep, reversal of these effects by a $5HT_{1A}$ antagonist has not been shown. In view of these references, one of ordinary skill in the art would not use a $5HT_{1A}$ antagonist to increase wakefulness (which is included in the instant sleep dysfunction). Indeed, Bjorvatn states that although 5HT has been implicated in the regulation of vigilance, whether 5-HT is important for sleep or waking processes remains controversial (Bjorvatn, abstract, first sentence).

b. ***Treating conditions that encompass seemingly opposite characteristics with the same compound.***

Appellants submit that it is not illogical to treat conditions that encompass seemingly opposite characteristics with the same compound because it is widely recognised that a therapy may serve to restore or ensure homeostasis with respect to a given physiological system, which can in turn remedy disorders that derive from an excess or a deficiency of a fundamental component of the system.

The examiner does not dispute that negative feedback is an important part of the homeostasis under physiological conditions. Indeed, the same compound may act both as an agonist and an antagonist and be useful in treating seemingly conflicting conditions. However, it is well-recognized by one of ordinary skill in the art that only under certain conditions would it elicit a certain response, while under a different set of conditions, the same compound would lead to a seemingly conflicting condition. Accordingly, teaching

and guidance setting forth the conditions for how and when to use the same compound for the opposing conditions would be required for one of ordinary skill in the art to use the compound without undue experimentation. In the instant case, the different critical conditions for the seemingly opposite responses have not been described in the specification, and the prior art does not remedy this shortcoming.

*c. **Sufficiency of representative examples establishing compounds of formula I as 5-HT_{1A} receptor antagonists.***

Appellants submit that they have presented representative examples that establish that the compounds of formula I are 5-HT_{1A} receptor antagonists, and the skilled artisan would accept the disclosed model assays as reasonably correlating to the claimed effects.

Contrary to Appellants' assertion that the objectively reliable character of in vitro assays presented in the specification has been ignored, the rejection has taken into consideration the data presented in the specification as one of the several evaluation factors on which the final conclusion is based.

Appellants maintain that it is not the presence or absence of a structural relationship between the known $5HT_{1A}$ receptor and the compound of the present invention, but rather the functional relationship that permits the appellants to provide compounds that utilize the nexus between the modulation of $5HT_{1A}$ receptor activity and the treatment of certain $5HT_{1A}$ receptor –effected medical conditions.

In response, it is the examiner's position that there is a high degree of unpredictability in the 5HT receptor antagonist art, that different biological activities are

exhibited by compounds of similar structures (Wijngaarden, Recl. Trav. Chim. Pays-Bas, 1993, 112:126-130, pages 129-130, Fig. 6, Fig. 7, Fig. 8) and that in vitro antagonism does not provide a predictable nexus to in vivo efficacy. One of ordinary skill in the art therefore would have little basis to extrapolate results from the tested compounds to other antagonist compounds of dissimilar structure. For example, the $5HT_{1A}$ antagonist, WAY 100635, by itself has no significant effects on feeding (Ebenezer et al), whereas the 5-HT_{1A} antagonist, (S)-UH-301, decreases palatable food consumption in rats by itself (Moreau et al.). (See paragraph a above). In view of the fact that the nexus between 5-HT_{1A} receptor antagonists and treatment of Alzeheimer's disease, appetite control, disorders of thermoregulation and sleep dysfunction has not been predictably established, and the breadth of the claims does not commensurate in scope with that of the objective enablement (paragraph a-b above), it is concluded that insufficient guidance and teaching have been provided in the specification to enable one of ordinary skill in the art to use the invention as claimed without undue experimentation.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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